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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/713,632

11/13/2003

Lawrence M. Kauvar

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EXAMINER

SHAW, AMANDA MARIE

ART UNIT

PAPER NUMBER

1634

MAIL DATE

DELIVERY MODE

04/25/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action  
Before the Filing of an Appeal Brief**

Application No.

10/713,632

Applicant(s)

KAUVAR ET AL.

Examiner

Amanda M. Shaw

Art Unit

1634

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 09 April 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.  
b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
(b) ☐ They raise the issue of new matter (see NOTE below);  
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

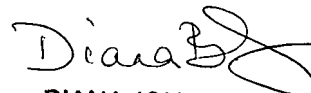
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.  
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
The status of the claim(s) is (or will be) as follows:  
Claim(s) allowed: none.  
Claim(s) objected to: none.  
Claim(s) rejected: 1-17.  
Claim(s) withdrawn from consideration: none.

**AFFIDAVIT OR OTHER EVIDENCE**

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.  
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_  
13. ☐ Other: \_\_\_\_\_

  
DIANA JOHANNSEN  
PRIMARY EXAMINER

Continuation of 5. Applicant's reply has overcome the following rejection(s): The rejection of claim 3 over the phrase "said first and second fluorophores" has been dropped in view of Applicants amendments to claim 2.

Continuation of 11. does NOT place the application in condition for allowance because: Continuation of 11. does NOT place the application in condition for allowance because: In the response filed April 4, 2007 Applicants argue that the phrase "wherein said method does not include a step of separating the target nucleic acid from non-target nucleic acid" is not new matter. The Applicants specifically state that since there is no separation described in Example 1, it should be apparent that none is required and that Applicants do not need to specifically state all the steps that are not taken. While applicants are not required to specifically state all of the steps that are not taken, the MPEP states that any negative limitation or exclusionary proviso must have basis in the original disclosure (See PEP 2173.05(i)). Further the applicant points to page 7 of the specification which states "the present invention offers highly sensitive ways to analyze a target nucleic acid without the need for physical separation steps" for support. These arguments have been fully considered but were not found persuasive. As explained in the Final Office action of February 9, 2007, the teachings on page 7 of the specification do not provide support for the claim language of "wherein said method does not include a step of separating the target nucleic acid from non-target nucleic acid" because the teachings could mean that the invention does not require the step of separating the target from the non target nucleic acids or it could mean that the invention does not require the step of separating unbound probes prior to detection or any other type of separation. For these reasons the new matter rejection is maintained.

Regarding the rejections made under 35 US 112 2nd paragraph, the Applicants argue that the phrases "observing by microscopy the presence or absence of proximity" and "whereby the presence of said proximity identifies said desired region" would be clearly understood by those skilled in the art. The applicants further state that in the methods of the instant invention what is observed is the presence of two labels as a pair. The applicants argue that a pair would be readily distinguishable from isolated occurrences of the label and that a skilled artisan would be able to detect which beads are paired and which are not. This argument has been fully considered but is not found persuasive. First of all the claims are not drawn to a "pair" of labels. The claims are drawn to "observing by microscopy the presence or absence of proximity of the first and second particulate labels". This phrase is considered unclear because "proximity" is not defined by the claim or the specification. For example it is unclear if the claims reads on probes which bind within 50, 100, 1000, or 10000 base pairs of each other. The claim could even encompass probes which bind at opposite ends of a chromosome. Without a definition of term "proximity" the metes and bounds of the claim are not clear. With respect to the phrase "whereby the presence of said proximity identifies said desired region", it is unclear how the presence of proximity is able to identify a region. Thus the rejection over claims 1-17 is maintained. It is also noted that the Applicants have amended claim 2 to overcome the rejection of the phrase "said first and second fluorophores" in claim 3. Therefore this rejection has been dropped.

Regarding the rejections made under 35 US 103, the Applicants argued that the combination of the Gray and Barbera-Guillem references are not suggested by the art, but by the invention itself, and that no motivation can be found to combined these documents, and that even if combined they fail to suggest the invention as claimed. Applicant's arguments have been fully considered but they are not persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Barbera-Guillem teaches several reasons why one would be motivated to modify the method of Gray. For example Barbera-Guillem teach that fluorescent nanocrystals are resistant to photo bleaching, share an excitation wavelength spectrum, and are capable of emitting fluorescence of high quantum yield with discrete peak emission spectra (Column 1). In the instant case Barbera-Guillem is using fluorescent nanocrystal labeled microspheres for fluorescence analysis. Barbera-Guillem et al further teach that these are superior to conventional fluorescent dyes because those dyes typically have a narrow excitation spectrum, it is hard to find a wavelength spectrum of light suitable for simultaneously exciting several different fluorescent labels, and they are susceptible to photo bleaching which limits the time in which a signal can be detected (Column 1). So clearly there are several advantages of using fluorescent nanocrystal labeled microspheres over conventional fluorescent dyes. Therefore one of skill in the art would have been motivated to have modified the method of Gray by using the labels suggested by Barbera-Guillem in order to achieve the benefits of using a fluorescent nanocrystal labeled microsphere rather than a conventional fluorescent dye. Additionally the Applicants state that the preamble is significant in that it imposes limitations on the method steps because the nature of the substrate that would be used in the assay set forth in the body of the claim. The Applicants further state that the substrate used in the instant invention would be different than the substrate used in Gray. First of all it is pointed out that the claims do not recite a particular substrate that is used. In the instant case the claims only require the two probes to bind to a desired region and the Gray reference teaches that. For these reasons the rejections made under 35 US 103 are maintained.